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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/476,485	12/30/1999	M. Gabriella Colucci	108.236.119	7906

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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 04/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/476,485	COLUCCI ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *73-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *73-80* is/are rejected.

7)☒ Claim(s) *81-83* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/19/04 has been entered.

Claims 73-83 are pending

2. The following is a quotation of the second paragraph of 35 U.S.C. 112.
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 73, 75-80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "hybridizing under stringent conditions" in claim 73 is ambiguous. Although the specification discloses on page 21 line 23 general parameters for calculating such conditions, in the absence of a clear definition of the metes and bounds of this phrase it is unclear which conditions are actually claimed.

It is suggested that Applicant amend the claims to recite a particular set of hybridization and wash conditions to overcome this rejection.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 73-80 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling a pharmaceutical formulation comprising a FRIL family member of progenitor cell preservation factors, wherein FRIL is D1 –FRIL (SEQ ID NO:2) from *Dolichos lab lab* or PV-FRIL (SEQ ID NO:6) from *Phaseolus vulgaris* or Yam-FRIL (SEQ ID NO: 8) from *Sphenostylis stenocarpa* that can be used to preserve progenitor cells does not reasonably provide enablement for a pharmaceutical formulation comprising a FRIL family member of progenitor cell preservation factors, wherein FRIL is encoded by a nucleic acid molecule that

hybridizes under stringent conditions to a nucleic acid having a nucleotide sequence complementary to a nucleotide sequence of SEQ ID NOs: 1,5 and 7, claimed in claims 73 or a pharmaceutical formulation comprising a FRIL family member of progenitor cell preservation factors, wherein FRIL has at least 95 % amino acid sequence identity to amino acid sequences of SEQ ID NOs : 2, 6 and 8, claimed in claim 74. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation.

(A) The claims as written encompass the genus of a FRIL family members. The genus encompasses peptides wherein such peptides have numerous differences in amino acid sequences.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

Applicant discloses only FRIL from *Dolichos lab lab that* is D1 –FRIL (SEQ ID No.2), or PV-FRIL (SEQ ID No.6) from *Phaseolus vulgaris* or Yam-FRIL (SEQ ID No. 8) from *Sphenostylis stenocarpa* in the instant specification (see page 56, line 3-9 ; page 83, line 25-30, and page 121, lines 5-11 . Applicant only disclosed a pharmaceutical composition comprising of D1 –FRIL (SEQ ID NO:2) or PV-FRIL (SEQ ID NO:6) or Yam-FRIL (SEQ ID NO: 8) that have a progenitor cell preservation activity (see Examples 1, 5, 10, 11 and 22 in particular). Applicant has not taught how to make and/or use a pharmaceutical formulation comprising a FRIL family member of progenitor cell preservation factors, wherein FRIL is encoded by a nucleic acid molecule that hybridizes under stringent conditions to a nucleic acid having a nucleotide sequence complementary to a nucleotide sequence of SEQ ID NOs: 1,5 and 7, claimed in claims 73 or a pharmaceutical formulation comprising a FRIL family member of progenitor cell preservation factors, wherein FRIL has at least 95 % amino acid sequence identity to amino acid sequences of SEQ ID NOs : 2, 6 and 8, c laimed in claim 74 that have progenitor cell preservation activity . The structural and functional characteristics of said peptides are not defined in the claim. The disclosure of SEQ ID NOS: 2, 6 and 8 cannot support the entire genus of FRIL family of progenitor cell preservation factors derived from plant lectins. In addition, Moore (US Patent 6,084,060) teaches that whether plant lectins act on mammalian cells via de novo means, or simply mimic their functional mammalian homolog is

not yet know. No lectin has been successfully developed as human therapeutics (see column 2, lines 24-30 in particular).

It is known in the art that even single amino acid changes or differences in a proteins amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama et al. (PNAS, 1993. 90: 10056-10060) teach that the human glycosylation factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (see Figure 1 in particular). Yet, Mikayama et al. further teach that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF activity (see Abstract in particular).

Applicant is relying upon certain biological activities and the disclosure of a limited number of species to support an entire genus. It is well known that minor structural differences among even structurally related compounds or compositions can result in substantially different biology, expression, and pharmacology of proteins. Therefore, structurally unrelated any FRIL encoded by a nucleic acid molecule that hybridizes under stringent conditions to a nucleic acid having a nucleotide sequence complementary to a nucleotide sequence of SEQ ID NOs: 1, 5 and 7, or any FRIL family member of progenitor cell preservation factors, wherein FRIL has at least 95 % amino acid sequence identity to amino acid sequences of SEQ ID NOs : 2, 6 and 8, claimed in claim 74 would be expected to have greater differences in their activities.

Since the amino acid sequence of a polypeptide determines its structure and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. binding of FRIL to a normally glycosylated FLT3 receptor, as stressed by Applicant is essential for the invention, see page 25, line 3-5 in particular) requires a knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification) and detailed knowledge of the ways in which a polypeptide's structure relates to it's functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain functional aspects the peptides and finally, what changes can be tolerated with respect thereto is complex and well outside the realm of routing experimentation.

Since the amino acid sequence of a polypeptide determined its structural and functional properties, predictability of which fragments will retain functionality requires knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence contribute to its structure, and therefore, function. The problem of predicting which fragments or derivatives of a protein will retain functionality and which will not is complex and well outside the realm of routine experimentation. Because of the lack of sufficient guidance and predictability in determining which structures would lead to functional proteins or peptides with the desired properties and that the relationship between the sequence of a peptide and it's tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al, in The Protein Folding Problem and Tertiary Structure Prediction, 1994. (ed.), Birkhauser, Boston, MA,

pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of proteins encompassed by the claimed invention.

In view of this unpredictability the skilled artisan would not reasonably expect a polypeptide having anything less than 100% identity over the full length of SEQ ID NO:2, 6 and 8 to *share the same function* as D1 –FRIL (SEQ ID NO:2) or PV-FRIL (SEQ ID NO:6) or Yam-FRIL (SEQ ID NO: 8) that have a progenitor cell preservation activity. Thus the recitation of percent identity language, in the absence of *a testable function* and limitations regarding the *sequence length over which the percent identity is required*; does not allow the skilled artisan to make and use the encoding nucleic acids commensurate in scope with the instant claims without undue experimentation.

Similarly, the fact that two nucleic acid sequences will hybridize under moderate or stringent conditions does not in and of itself require that the two sequences share any functional activity. Thus the same observations apply to the recitation of " a nucleic acid molecule that hybridizes under stringent conditions to a nucleic acid having a nucleotide sequence complementary to a nucleotide sequence of SEQ ID NOs: 1, 5 and 7", claimed in claims 73 as were noted above with respect to "percent identity" language. Further, it was well known in the art at the time the invention was made that hybridization could occur between two sequence based upon short stretches of 100% identity. Thus a great deal of sequence variability *with respect to the full-length nucleic acid* is possible and in the absence of a clear recitation that the identity is over the full length of SEQ ID NOs:1 5 and 7 , the claim reads on subsequences and would be viewed by the skilled artisan as been even less likely to encode a polypeptide with the same function as FRIL proteins encoded by SEQ ID NOs:2 , 6 and 8. Finally, hybridization under conditions other than high stringency would be expected to permit a great deal of variation between the two hybridizing sequences, making it even more unpredictable that the two sequences would share the same function. Thus as for the recitation of percent identity, hybridization language in the absence of *a testable function* and limitations regarding both the *hybridization conditions* and the *sequence length over which the hybridization takes place*; does not allow the skilled artisan to make and use the hybridizing nucleic acids commensurate in scope with the instant claims without undue experimentation.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed a pharmaceutical formulation comprising a FRIL family member of progenitor cell preservation factors, wherein FRIL is encoded by a nucleic acid molecule that hybridizes under stringent conditions to a nucleic acid having a nucleotide sequence complementary to a nucleotide sequence of SEQ ID NOs: 1,5 and 7, claimed in claims 73 or a pharmaceutical formulation comprising a FRIL family member of progenitor cell preservation factors, wherein FRIL has at least 95 % amino acid sequence identity to amino acid sequences of SEQ ID NOs : 2, 6 and 8, claimed in claim 74 in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

5. Claims 73-80 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of : a pharmaceutical formulation comprising one members of the FRIL family of progenitor cell preservation factors, wherein FRIL is D1 –FRIL (SEQ ID NO:2) from *Dolichos lab lab* or PV-FRIL (SEQ ID NO: 6) from *Phaseolus vulgaris* or Yam-FRIL (SEQ ID NO: 8) from *Sphenostylis stenocarpa* that can be used to preserve progenitor cells .

Applicant is not in possession of : a pharmaceutical formulation comprising a FRIL family member of progenitor cell preservation factors, wherein FRIL is encoded by a nucleic acid molecule that hybridizes under stringent conditions to a nucleic acid having a nucleotide sequence complementary to a nucleotide sequence of SEQ ID NOs: 1,5 and 7, claimed in claims 73 or a pharmaceutical formulation comprising a FRIL family member of progenitor cell preservation factors, wherein FRIL has at least 95 % amino acid sequence identity to amino acid sequences of SEQ ID NOs : 2, 6 and 8, claimed in claim 74.

The specification fails to described which core structure of a FRIL family of progenitor cell preservation factors is essential for maintain its biological activity , i.e. to preserve progenitor cells and define all members of the an essentially pure FRIL family of progenitor cell preservation factors . The lack of sufficient limitations would therefore allow for all other FRIL family members. Therefore, the skilled artisan cannot envision all the contemplated FRIL possibilities recited in the instant claims.

A description of a protein by functional language in the absence of a structure is not considered sufficient to show possession of the claimed invention. See Fiers, 984 F.2d at 1169-71, 25 USPQ2D at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. Many species may achieve that result. The definition requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 /f.2d 1516, 1521, 22 USPQ 369, 372-73 (Fed. Cir. 1984) affirming the rejection because the specification does "little more than

outline[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what the material consists of (e.g. structural feature), is not a description of that material.

Applicant has disclosed a limited number of species; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

A description of a genus of FRIL family members sequences may be achieved by means of a recitation of a representative number of polypeptide sequences, defined by amino acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

6. Claims 81-83 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

7. No claim is allowed

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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